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AAPS/RAPS/CAPRA Collaborative Program: Exploring the Challenges of Drug Regulation in a Global Environment: Clinical Concerns

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ABSTRACT

Globalization of the pharmaceutical industry has led to a need to harmonize the regulatory requirements governing the marketing of medicinal products. To minimize the barriers impeding global drug product registration, the International Conference on the Harmonization of Technical Requirements of Pharmaceuticals for Human Use (ICH) was established in 1990. The ICH has developed a series of guidelines that reflect agreements reached by participating nations on aspects of the chemistry and clinical technical sections that will fulfill the regulatory requirements of these various jurisdications. Nevertheless, there continue to be points of divergent perspectives and barriers that can impede the use of foreign clinical data. Given the importance of these issues, the Regulatory Science (RS) section of the American Association of Pharmaceutical Scientists (AAPS), in conjunction with the Regulatory Affairs Professional Society (RAPS) and the Canadian Association of Professional Regulatory Affairs (CAPRA) cosponsored a public forum on this topic. This manuscript provides a summary of the speaker presentations and audience discussions regarding the design of clinical trials and the extrapolation of results from these trials to support international drug registration.

KEYWORDS: clinical trials, regulatory requirements, international harmonization, foreign clinical data

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INTRODUCTION

The globalization of the pharmaceutical industry led to the need for harmonizing the regulatory requirements governing the marketing of medicinal products. Through these harmonization efforts, the time and cost efficiency of pre-approval activities has been improved, while duplication and redundancy have been minimized. The formalization of these efforts can be found in documents published by the International Conference on the Harmonization of Technical Requirements of Pharmaceuticals for Human Use (ICH) (http://www.ich.org/) (date accessed, August 2003). The ICH was first organized in 1990 and includes the regulatory authorities of Europe, Japan, and the United States, as well as technical experts from the pharmaceutical industries of those and other countries (such as Canada). Its mission is to identify ways to ensure the economical use of human, animal, and material resources, and to eliminate unnecessary delays in the global development and availability of new medicines. The ICH has produced a variety of guidelines covering topics relating to chemical and pharmaceutical quality assurance, the design of in vitro and in vivo preclinical studies for evaluating drug safety (eg, carcinogenicity, genotoxicity testing), and the design of protocols for evaluating drug clinical effectiveness in human subjects. Under the topic heading of efficacy, there are 12 guidelines that have been implemented (www.ICH_Guidelines_Efficacy.htm) (date accessed August 2003). A summary of these guidelines, as described on the ICH Web site, is provided in the appendix.

Typically, during the guideline development process, each participating country provides its own set of standards and regulations governing the design, analysis, and evaluation of clinical trials. These are subsequently integrated or amended in line with ICH. Nevertheless, when pursuing a global marketing strategy, there continue to be region-specific issues that drug sponsors need to consider, such as the following:

- Canada: Division 5 of the Food and Drugs Regulations defines Clinical Trial Application requirements and is consistent with ICH Guidelines for clinical trials. Nevertheless, sponsors need to pay attention to details defined under Division 8, which is the section of the regulations concerning the information considered in review of the trials. In addition, there are several specific guidances or policies that need to be kept in mind, such as those associated with oral contraceptives[1] and topical non-steroidal inflammatory drugs.[2]
- Europe: While the ICH guidelines on efficacy have been adopted, the European Agency for the Evaluation of Medicinal Products (EMEA) Web site contains a number of guidance documents (final and draft), as well as manuscripts containing points to consider. These documents provide further advice on specific disease treatments, trial design recommendations, and study acceptance criteria for such conditions as asthma,[3] acute stroke,[4] and schizophrenia.[5]
- United States: In a Food and Drug Administration (FDA) guidance dated 03/01, *Acceptance of Foreign Clinical Studies*, which was co-authored by experts in the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), and the Center for Devices and Radiological Health (CDRH), it states that FDA regulations permit the acceptance of foreign clinical studies in support of an application for marketing approval of a human drug, biological product, or device if certain conditions are met. Foreign studies performed under an investigational new drug application (IND) or investigational device exception (IDE) must meet the same requirements of 21 Code of Federal Regulations (CFR) 312 or 21 CFR 812, respectively, that apply to U.S. studies conducted under an IND and IDE [21 CFR 312.120].

21 CFR 312.120 specifically details regulations governing the use of foreign clinical studies not conducted under an IND. Among the listed concerns is that the study must be adequate and well controlled as defined under Sec. 314.126 and must be in conformance with ethical principles as stated in the "Declaration of Helsinki."

To appreciate some of the barriers to using foreign data to support the registration of a medicinal product for human use, we should consider the characteristics of an adequate and well controlled study, such as that described in US 21 CFR 314, and ICH guidance documents E3, D6, and E8:

1. There is a clear statement of the objectives of the investigation and a summary of the proposed or actual methods of analysis in the protocol for the study and in the report of its results.
2. The study uses a design that permits a valid comparison with a control to provide a quantitative assessment of drug effect. Generally, the following types of controls are recognized:
   (a) Placebo concurrent control.
   (b) Dose-comparison concurrent control. At least 2 doses of the drug are compared.
   (c) No treatment concurrent control. Where objective measurements of effectiveness are available and placebo effect is negligible, the test drug is compared with no treatment.
   (d) Active treatment concurrent control. The test drug is compared with known effective therapy.
   (e) Historical control.
3. The method of selection of subjects provides adequate assurance that they have the disease or condition being studied, or evidence of susceptibility and exposure to the condition against which prophylaxis is directed.
4. The method of assigning patients to treatment and control groups minimizes bias and is intended to assure comparability of the groups with respect to pertinent variables such as age, sex, severity of disease, duration of disease, and use of drugs or therapy other than the test drug.
5. Adequate measures are taken to minimize bias on the part of the subjects, observers, and analysts of the data. The protocol and report of the study should describe the procedures used to accomplish this, such as blinding.
6. The methods of assessment of subjects' response are well defined and reliable.

To minimize international differences in study design, the ICH E8 document titled *General Considerations of Clinical Trials* details internationally accepted principles in clinical trial conduct and drug development. This guidance represents an effort to promote a common understanding of general clinical trial principles. The ICH E6 document titled *Good Clinical Practice (GCP) Consolidated Guideline* provides a unified standard for designing, conducting, recording, and report-

ing clinical trials and ensures that subjects' rights and well-being are protected.

Despite efforts for international harmonization, there continue to be regional differences in treatment effects that can occur, even if an investigation strictly conforms to conditions consistent with a well-controlled clinical trial. For example, international differences in patient characteristics and sociological factors can markedly influence product efficacy. Such was the case when eptifibatide was administered to patients following acute myocardial infarction (MI). North American patients tended to be younger, weigh more, and have a higher frequency of diabetes as compared with their European counterparts. Environmental factors such as diet, alcohol consumption, genetics (such as attributes of patient coagulation and fibrinolytic pathways), the frequency and type of intervention procedures employed, and international differences in accurately diagnosing an acute MI further contributed to an international disparity in conclusions regarding drug response.[6]

Ethnic factors have also been recognized to largely influence patient outcome. For this reason, the National Institute of General Medical Sciences (NIGMS) of the US National Institutes of Health has established a nationwide research network to identify those ethnic differences that can affect both the pharmacokinetics and pharmacodynamics of a drug.[7,8] For example, black patients tend to have a poor response to the antihypertensive effects of beta blockers and angiotensin-converting enzyme inhibitors. Therefore, inclusion of these subjects in positive controlled clinical trials to test a new antihypertensive agent could bias the results in favor of the investigational new drug.[9] In addition, African populations demonstrate a higher frequency of major bleeding events after the use of tissue plasminogen activator (tPA) as compared with that observed with other ethnic groups.[10]

Medical terminology itself can be a potential roadblock to harmonization efforts. For example, during a survey of randomized clinical trials providing a global examination of effective therapeutic interventions for sepsis (a total of 74 studies published in any language from 1966 to 1998), it was noted that very different definitions of sepsis were employed among the various geographic regions.[11] Moreover, a requirement for the microbiological confirmation of an infection was not found in any of the 74 trials, although 15 mortality-based and 6 surrogate outcome trials did require documentation of objective clinical evidence of infection. In 8 of the trials, no explicit definition of sepsis was provided. Clearly, such marked differences could significantly influence study design, endpoints, and outcomes.

To overcome this potential barrier to the use of foreign data, the ICH has been involved in the development of an international standard for medical terminology. It was agreed that an international terminology would be based upon the European Union (EU) system, MedDRA (Medical Dictionary for Drug Regulatory Affairs). Consequently, MedDRA has become the new global standard medical terminology and has been adopted by the major global regulatory authorities (United States, Europe, and Japan). The FDA, for example, has already implemented MedDRA within its Adverse Event Reporting System (AERS). European authorities are beginning to use MedDRA as a key part of their electronic database systems.[12]

The next step in these harmonization efforts is attaining consensus on what constitute appropriate therapeutic endpoints. For example, in the evaluation of treatments for chronic peripheral arterial occlusive disease (a marker of generalized atherosclerosis), the goals of therapy can vary from the simple prevention of mortality to something as difficult to quantify as quality of life. Factors such as the presence of concurrent illness, lifestyle, and life expectancy all influence treatment decisions, trial design, and consequently, drug effectiveness. Differences in judgment further affect trial design by influencing decisions on whether it is preferable to base a determination of effectiveness on the use of statistical (eg, statistically significant differences) versus clinical endpoints (predefined deltas and composite endpoints). Within the European Regulatory Agency, guidelines have been issued in an attempt to develop a unified drug development process within the countries of the EU.[13]

Although foreign clinical trial data may be acceptable, study results need to be examined in the context of medical practice and health care standards in each country. While the data obtained may be universally applicable, the interpretation may and likely will vary in each jurisdiction. In this regard, factors to consider include:

1. Cultural views of human welfare and quality of life issues.
2. Approaches to medical practice, including
   (a) The quality of clinical encounter between patient and attending physician.
   (b) The use of surgical interventions.
   (c) Regional philosophy governing the types and frequency of pharmaceutical intervention.

(d) Use of concomitant medications.

(e) Use and availability of alternative therapies.

(f) The use of diagnostic test procedures.

(g) Length of stay in hospitals, intensive care units, and the quality of post-treatment care.

(h) Expectations with regard to the level of care.

(i) Populations access to medical treatment (ie, the existence of subpopulations less likely to receive high quality medical care).

3. Financial reimbursement policies.
4. The skill level of the attending physicians.
5. Quality of records.

Further confounding the applicability of clinical data across geographic regions and cultures are the host of physiological and environmental variables that can affect the clinical effectiveness of a therapeutic intervention. These variables include:

1. Genetic factors (pharmacogenetics).
2. Diet.
3. Use of tobacco and alcoholic beverages.
4. Level of exercise.
5. Environmental factors (including hygiene, stress, support networks, pathogen exposure/susceptibility patterns).
6. Baseline factors (such as weight, age and gender, concomitant diseases or physiological conditions).
7. Use of concomitant medications (polypharmacy).
8. Use of alternative medicine or therapies.
9. Cultural views on life and death issues.
10. Nature of the disease (eg, the extent of cardiac occlusion).

Thus, despite efforts toward global harmonization, there remain valid concerns about the mutual use and acceptance of foreign clinical study data. In some instances, international differences in standards can be resolved through continued debate and with the development of compromises that maintain safeguards on quality, safety, and efficacy. However, for those instances where patient physiological and societal dictates are the basis for design discrepancies, studies may need to be repeated in more than one region. In those cases, it will be impossible to avoid apparent redundancy and study duplication without potentially compromising product performance within certain promising product performance within certain patient subpopulations.

Given the impact of these issues on drug regulation, medical practice, pharmaceutical development and public health, the Regulatory Science (RS) section of the American Association of Pharmaceutical Scientists (AAPS) initiated a public forum for exploring these issues. Using the format of a satellite workshop to the AAPS annual meeting in Toronto, Canada, the RS section collaborated with the Canadian Association of Professional Regulatory Affairs (CAPRA) and the Regulatory Affairs Professional Society (RAPS) to launch this interactive event. Each organization brought its unique perspectives to the development of the workshop agenda, selection of speakers, and the subsequent discussion of issues.

This manuscript attempts to capture the information conveyed during the speaker presentations and audience discussions. We have tried to expand upon these points by referring to key published manuscripts. Nevertheless, to ensure consistency with the speaker's intended message, each presenter was provided an opportunity to critique this manuscript.

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To encompass a wide range of topics, the meeting was divided into parallel clinical and chemistry/manufacturing sessions. Invited experts shared their insights into mechanisms for maneuvering through the maze of international drug regulatory requirements and underlying scientific challenges. The subsequent breakout sessions provided participants with the opportunity to share experiences, express opinions, and consider potential solutions to factors impeding product globalization.

Clinical Trials: Globalization of Requirements: Pros and Cons

Benefits and Mechanisms for Increasing the Efficiency of Drug Product Development Through International Harmonization

Karen L. Goldenthal, Director, Division of Vaccines and Related Products Applications, Center for Biologics Evaluation and Research, United States FDA.

The ICH was established in 1990 to bring together regulatory authorities of the EU, Japan, and the United States, as well as experts from the pharmaceutical industry in these 3 regions. The purpose of ICH is to harmonize the technical requirements for registration of new drugs and thus to streamline the development process. This lecture covered aspects of ICH documents E5, E6, and E8.

The ICH E6 document entitled *Guideline for Good Clinical Practice* was finalized in May 1996 and published in the *Federal Register* in May 1997. This document is clearly a cornerstone for successful international harmonization of clinical trial requirements. While there are many benefits to implementing GCPs, this activity takes resources and may require modifications to the approach to clinical research. One example of implementation of updated GCPs based on the published observations of some Japanese authors was discussed.[14] The Organization for Pharmaceutical Safety and Research (OPSR) is responsible for domestic GCP audits in Japan. Audits conducted by OPSR from 1997 through 2000 identified problems including a high prevalence of deficiencies with case report forms (CRFs), eg, incorrect descriptions of concomitant medications, as well as deficiencies with the informed consent (IC) forms. The authors observed that the basis for some of these problems was cultural. For example, multiple drug use, which can lead to use of prohibited concomitant medications, was preferred by Japanese physicians. This preference could have an impact on CRFs and adherence to exclusion criteria. Also, as noted by the authors, some problems observed during this transition period were the result of a number of historic Japanese administrative practices: (1) CRFs were often completed solely by investigators without help from other staff; (2) there was a lack of professional research coordinators and research nurses; (3) written IC was recommended, but not required; and (4) there was often a lack of on-site monitoring by sponsors. Of interest, the Japanese regulations focus more on the responsibility of the sponsor,[14] whereas in the United States, serious departures from guidelines could lead to penalties being imposed upon the clinical investigator.

The ICH E5 document entitled *Ethnic Factors in the Acceptability of Foreign Clinical Data* was discussed. One goal of this document is to minimize the duplication of clinical studies, especially resource consuming clinical endpoint efficacy trials. In particular, the use of bridging studies, which may be needed to extrapolate safety and efficacy data to different populations due to differences in intrinsic and extrinsic factors, were discussed. It was noted that an ICH steering committee agreed to establish an implementation work group (IWG) to further clarify the interpretation of the E5 document.

Accepting foreign clinical data to support approval in new regions is critical in many areas of drug development. For example, foreign efficacy trials have played an important role in the licensure of some preventive vaccines for infectious disease indications. Foreign trials can have an important role in the development of vaccines when epidemiology limits or precludes conducting clinical endpoint trials within the United States (eg, traveler's vaccines, such as Japanese encephalitis virus vaccine). However, it is recognized that immunogenicity (and efficacy) differences between populations may result from differences in factors such as genetics, nutritional status, and background infections. Overall, for example, trivalent live, oral poliovirus vaccine had lower immunogenicity and efficacy in developing countries compared with developed countries.[15] Thus, the safety and immunogenicity of candidate vaccines in the target population is of interest. Validated assays to

assess immune responses are critical to the interpretation of bridging studies.

One topic of discussion was regional differences in efficacy results observed within so called "megatrials." Large multinational trials can provide a huge patient base and thus facilitate quick and cost-effective study completion.[16,17]

For example, for myocardial infarctions (MIs), there are relatively low hazard rates for short-term outcomes to assess treatment effect, especially a low death rate, and a large trial can arrive at an answer regarding the efficacy of an intervention in a timely manner. However, regional differences in efficacy have been observed in some trials.[16,17]

A case in point is the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) megatrial. PURSUIT was a double-blind, randomized, placebo-controlled study in 10 948 patients presenting with acute coronary syndromes without persistent ST-elevation. This trial enrolled patients in Western Europe, Eastern Europe, North America, and Latin America. Subjects were randomized to 1 of 3 groups: 2 groups received eptifibatide, a platelet glycoprotein IIb/IIIa inhibitor (with 2 different regimens, respectively), and 1 group received placebo. The primary endpoint was a 30-day composite of death or MI. This was a real world study; each patient was managed by usual site standards. In this regard, the frequencies of angiography, percutaneous coronary intervention, and coronary artery bypass grafting differed widely from site to site and country to country.

Overall for this trial, there was a statistically significant benefit for the use of eptifibatide. However, marked regional variations were observed in the treatment response.[18] For example, patients from North America experienced the greatest treatment benefit from this intervention. In contrast, no apparent treatment effect was observed in the subgroups of patients from Latin America or Eastern Europe. However, the confidence intervals (CIs) were wide and overlapping for these regional differences.

Of interest, an analysis suggests that these regional efficacy differences in the PURSUIT trial can be largely explained by differences in patient demographics and adjunctive treatment strategies as well as by methodology of MI definition and adjudication.[19] Limitations for the interpretation of subgroup data were also noted.[18]

Another example of interest here pertains to 2 trials with conflicting results when using the same type of vaccine. In these trials, infants were inoculated with a disease-specific prion protein vaccine to investigate its efficacy against *Haemophilus influenzae* type b (Hib) disease.[20] While 90% (95% CI: 70%-96%) efficacy was observed when the vaccine was studied in Finland, the vaccine did not demonstrate statistically significant efficacy when tested in a separate efficacy trial in Alaska (vaccine efficacy = 43% [95% CI: -43%-78%]).

The cause of this disparity is unclear. According to one source, this does not appear to involve either regional differences in product immunogenicity or subject race/ethnicity (similar results were seen across racial groups in the Alaskan study).[20] Some have postulated that the exposure to Hib in Alaskan infants (compared with Finnish infants) was more frequent, more intense, or both, which affected the efficacy observed.[20] The results observed in the Alaskan efficacy trial contributed to this particular Hib vaccine not being marketed within the United States for use in young infants.

Dr. Goldenthal emphasized that one of the most important first steps to take when considering the use of foreign data to support the registration of a human drug or biologic is to interact with the US FDA early and often during the product development process. She recommended that sponsors should not initiate clinical efficacy trials without obtaining prior concurrence from the FDA if the goal is to use such data to support licensure in the United States.

In summary, clear progress has been made toward harmonization of clinical trial requirements, especially with regard to the ICH clinical trial documents. Harmonization has benefits for both developed and developing countries. Harmonization can help to avoid duplication of effort and make evaluation of the trial results easier. Also, documents such as E6 are very valuable, as GCP issues can not be fixed after the fact. However, there is the recognition that harmonization will take resources and will not resolve all approval issues.

Selecting Treatment Controls

Patricia Huston, MD, Acting Senior Medical Advisor, Therapeutic Products Directorate Health Canada, and Project Director, National Placebo Initiative

The definition of an acceptable risk/benefit ratio may differ greatly between regions, thereby impacting the type of control used in a clinical investigation. The ICH Topic E10, lists several potential types of control groups. These include:

1. No-treatment (placebo) control.

2. Dose-response concurrent control.
3. Active control.
4. External control (which includes historical controls).

Selecting an appropriate control treatment is a principal challenge in the development of a clinical study design. The choice of control group affects the potential sources of interference, the method of patient and investigator blinding, subject randomization, ethical acceptability of the data, the ability to recruit subjects, the nature of the endpoint to be studied, and the choice of statistical analysis. A poorly selected control treatment that results in inconclusive data can lead to a failure to fulfill the requirements for "good" science. Alternatively, an inappropriate control treatment may contradict a region's standard of medical ethics and betray patient trust.

Placebo Control Trials

The difference between a placebo control and a no-treatment control is that a no-treatment control implies that the investigator is not blinded to treatment assignment. The latter approach is used only when, for whatever reason, it is impossible to blind the investigator.

Placebo control trials are generally considered unacceptable unless there are no effective alternative treatments available, if the available treatments can be highly toxic, or if the failure to administer alternative therapies is associated with "no risk of serious harm". With regard to the latter, a complicating factor in the development of placebo control trial protocols is that there can be substantial international differences with regard to the definition of "serious harm." Moreover, the definition itself may be a function not only of the disease condition being treated but also of the duration of the placebo treatment. In some cases, studies may allow for the use of palliative treatments, such as analgesics and escape measures, thereby allowing for rescue as needed.

Differences between international guidelines have resulted in a lack of consensus and an increasing scrutiny of studies designed with the use of placebo controls. These differences are summarized below:

- Declaration of Helsinki clarification. This document limits placebo-controlled trials to "minor conditions," where the patient is not subject to "serious or irreversible harm" or to studies with compelling and scientifically sound methodological reasons for using a placebo control group.
- World Health Organization's Council of International Organizations of Medical Sciences (WHO'S CIOMS) Guidelines. This guideline states that placebo controlled trials are ethically unacceptable if withholding an established treatment will result in more than a temporary discomfort or if it will increase the risk of serious or irreversible harm. It is also unacceptable to use a placebo control if an accepted positive treatment control would yield scientifically acceptable results.
- ICH E10. This ICH guideline states that placebo-controlled trials are generally considered ethical when there is no risk of serious harm, even if a patient may experience discomfort. However, withholding treatment must not lead to any risk of serious harm, and all patients need to be fully informed with regard to the availability of other treatments and the consequences of delaying treatment. The ICH E10 guidance further states that a placebo control treatment does not necessarily imply a lack of treatment, since in many placebo-controlled trials, the new treatment and placebo are added to a common standard therapy (known as add-on studies).
- Tri-Council Policy Statement (Canada). Placebo controls in clinical trials are "generally unacceptable" when standard treatments are available.

At this time, within Canada, there is no consensus on what constitutes appropriate placebo use; regulatory policy is based on ICH E10, whereas research ethics board policy is based on the Tri-Council Policy Statement. Therefore, a National Placebo Working Group (NPWG), cosponsored by Health Canada and the Canadian Institutes on Health Research, is attempting to achieve a consensus opinion in Canada on "what constitutes ethical and scientifically appropriate placebo use." In cross-Canada focus groups organized by the NPWG, 90% of the general public was found to support the use of placebos when there is no risk of serious harm, patients are informed of alternative treatments and potential risks, and patients are intensively monitored for the onset of adverse events. In addition, in-depth interviews are planned for patients who have participated in placebo-controlled trials. Based on these public consultations and input from major stakeholders, including patients, the NPWG is

scheduled to draft a report in early 2003. Final recommendations are scheduled for the end of 2003.

Ultimately, the acceptability of placebo-controlled trials should be based on a risk/benefit analysis. For example, now that bisphosphonates are available, are placebo-controlled studies in osteoporosis acceptable? The answer would be a qualified yes in patients with no history of vertebral fractures. However, the risk/benefit analysis would also be dependent on the duration of the study and the endpoints.

During the audience discussion, it was noted that the use of placebo control groups for studies on antidepressant therapies is one of the more contentious issues in this debate. The basic question is whether or not it is ethical to withhold a proven antidepressant therapy from a depressed person. It was noted that in antidepressant studies, the placebo response is usually high and depressed adult patients are able to request alternative therapies if necessary. For this reason, many regions allow for the use of placebo-controlled trials for antidepressants, so long as the enrolled patients are not at high risk, are closely monitored, and the trial is for a short duration. Additional discussion in this regard is provided below (positive controls).

The use of placebo-controlled antidepressant studies in adolescents/children is a far more challenging issue. One option is to try a new antidepressant medication in adolescents who have discontinued a first line therapy because of partial effectiveness or because of adverse effects. In this regard, it is recognized that tricyclic antidepressants generally do not work well in children. This may offer an alternative to those who would consider it unethical to do a placebo-controlled trial of an antidepressant in "treatment naïve" adolescents.

Positive Control Trials

When electing to use a positive control trial, there are several important questions that must be addressed:

1. Which active control should be selected when multiple therapies are available? Selection of the positive control represents a potential way to manipulate the study results.
2. If dosing occurs in another geographic region, is an optimal dose being administered to the patient population? For example, black patients are more resistant than Caucasian patients to the antihypertensive effects of β-blockers. Therefore, if a largely black population is enrolled in the study and the positive control is a β-blocker, the control group may be exhibiting little more than a placebo effect.
3. If a positive control clinical trial is being conducted in a foreign country, are differences in drug bioavailability/formulation accounted for? This could affect the delta (observed difference) between responses to the positive control versus the test product.
4. Responses to certain therapies (eg, antidepressants) are very subjective and therefore difficult to evaluate. Therefore, there are some conditions for which marked international differences may exist in the definition of what constitutes a significant clinical outcome. Moreover, these types of trials may include patients who were unresponsive to prior therapies, resulting in highly variable response frequencies. In these situations, trials may need to be conducted using a 3-arm study design (treatment, placebo, and positive control).

ICH E10 recommends trials designed to test superiority against active control treatments whenever possible. However, as acknowledged by E10, it is not always possible to have double-blinded active control trials. In addition, the criteria for substantial evidence of effectiveness may be highly subjective. Consequently, a sequential approach may also be performed within the context of the same study, where Level 1 would be considered superiority and Level 2 would be noninferiority. In the latter situation, the delta for an interim analysis, and a criterion for noninferiority, must be defined a priori (CPMP: points to consider on switching between superiority and noninferiority).[21]

Antidepressant trials are examples of where an active control noninferiority trial may fail to provide compelling evidence of efficacy due to a high placebo response rate and a variable treatment response rate. Numerous antidepressant trials have been unable to demonstrate a difference between the active treatment and the control.[22] In particular, it is important to know that the patients enrolled in the trial are not unresponsive to the control therapy. Investigators need to have the information upon which to determine if treatment superiority is a generalized phenomenon or whether superiority occurs primarily in patients previously shown to be unresponsive to existing alternative therapies. Because of the relatively high failure rate of antidepressant studies, a placebo group is often necessary to assess study sensitivity (discriminatory power) of the study. An example of this is the comparison of St John's Wort versus sertraline.[23] By including a placebo control arm in a double-blind, randomized trial involv-

ing 340 patients with major depression, it was demonstrated that neither drug outperformed the placebo.

The use of a positive control also necessitates an assessment of treatment differences with respect to the timing of drug impact on the progression of a disease. Therefore, the choice of endpoint and the scheduling of evaluations must be carefully weighed. In this regard, the E10 document points to 2 examples:

1. The use of thrombolytics in patients with acute myocardial infarction may reduce patient mortality but can also increase the risk of hemorrhagic stroke.
2. When evaluating an analgesic, there may be differences in both the intensity of effect and the duration of effect.

Historical Controls

Historical controls are an external form of control group, as contrasted to positive and placebo controlled trials that are internal control groups. As a result, there are a number of concerns that must be addressed to ensure that the treatment comparison remains unbiased. These include[24]:

1. Similarity of patient populations.
2. Similarity of ancillary care.
3. Accuracy of records.
4. Comparability or response assessments.

The historical data may have been generated at an earlier time or may be generated concurrently but within other settings (ie, concurrent control group). Because of the lack of randomization procedures, it is necessary to ensure that patients selected for historical (concurrent) controls do not represent individuals that are either refractory to therapy or unable to tolerate therapy.[24] Particularly when basing the comparison on general medical knowledge of clinical outcomes, it is imperative that the patient status be comparable, with considerations extending well beyond a simple comparison of the baseline measurements. Nevertheless, historical controlled trials may be particularly valuable for studies involving patients with life-threatening illnesses. In these cases, it is often considered unethical to withhold a possible remedy from patients, rendering placebo-controlled trials unacceptable.[25]

Ethnicity and Environmental Factors in the Acceptability of Foreign Data

Richard Anderson, MD, PhD, National Institute of General Medical Sciences, National Institutes of Health

Scientists are becoming increasingly aware of the importance of genetic factors in determining the effectiveness and toxicity of medications.[26,27] An early example of reported interindividual variability was by Pythagoras in the fifth century BC, when he noted that the ingestion of fava beans is harmful to some individuals but innocuous to others.[28] The toxic response to fava beans was found to be attributable to the development of hemolytic anemia in individuals deficient in erythrocyte glucose 6-phosphate dehydrogenase activity. Deficiencies in this same enzyme were found to be responsible for the occurrence of hemolysis after antimalarial therapy in individuals.[29] Another example, from the 1950s, includes the observed exaggerated effects of suxamethonium on muscle relaxation when administered to individuals deficient in plasma cholinesterase activity, and the development of peripheral neuropathies in individuals unable to acetylate isoniazid.[27] Since that time, it has been recognized that both intrinsic and extrinsic factors can affect patient responses, and that these factors can influence the outcome of clinical trials used to support product registration. The successes of the Human Genome Project and of the Single Nuceotide Polymorphs (SNP) consortium (http:/smp.cshl.org/) offer a basis for pharmacogenomic research.

When discussing issues pertaining to pharmacogenetics, several closely related terms need to be clarified. These include:

- Ethnicity versus genetic variation: Ethnicity refers to populations with common traits, customs, and shared ancestry. Genetic variation refers to subpopulations within an ethnic group. Most genetic variants are the same across all ethnic groups, but there are differences that occur in the polymorph frequency. Currently, there has been much difficulty in attaching any clinical significance to many of these variations.
- Pharmacogenomics versus pharmacogenetics: Pharmacogenomics deals with protein products and mechanisms. Pharmacogenetics deals with the actual genetic material.

The ICH E5 document[30] summarizes ethnic factors impacting therapeutic outcomes.

A. Intrinsic Factors

1. Generic

a. Gender

b. Race

c. Metabolic polymorphism
d. Genetic diseases

2. Physiologic and pathological conditions
   a. Age
   b. Organ functions (liver, kidney, cardiovascular)
   c. Disease

3. Genetic + physiologic
   a. Height
   b. Weight
   c. Receptor sensitivity

B. Extrinsic Factors
   1. Environment
   2. Socioeconomics
   3. Medical practices
   4. Drug compliance
   5. Regulatory practices
   6. Endpoint/methodology

There are numerous examples whereby these sources of variability have been observed to impact the clinical response to pharmaceutical interventions:

- In a study of the genetic determinants of the response of Mexican Americans to antidepressant medications, it was noted that only 60% to 65% of patients within this group responded to antidepressants.[31] However, the relative influence of variables such as pharmacokinetics, pharmacodynamics, and socioeconomic factors contributing to this subjective response was not determined.
- Pharmacogenetic factors may influence the effectiveness in bronchodilator response by asthmatics. There appear to be specific alleles associated with variations in bronchodilator response.[32,33,34]
- Differences in antihypertensive response to β blockers and hydrochlorothiazide can be separated into racial and genetic components. The black population within the United States is associated with a high incidence of hypertension. However, that relationship may be largely environmental as there is a far lower incidence of hypertension among black Africans (with the exception of some urban centers).[35] The susceptibility of the black population to hypertension and resistance to some types of antihypertension treatments is well documented.[36] Pathophysiological mechanisms suggest that the frequency of salt-sensitive blood pressure is also more common in black patients. However, while black patients tend to be more responsive to thiazide diuretics than their Caucasian counterparts, they simultaneously tend to be less responsive to monotherapy with angiontensin converting enzyme inhibitors.

The blurring of causative factors (intrinsic versus extrinsic variables) is clearly seen when examining differences in the frequency of hip fractures among different cultures and ethnic groups.[37] The incidence of hip fractures is substantially higher in females as compared with males. There is also a lower incidence of hip fractures in Asian Americans as compared with Caucasian Americans. While this point alone suggests intrinsic differences in bone strength, it was also noted that Asian immigrants to the United States developed a higher incidence of hip fractures compared with those in their countries of origin, with trends becoming increasingly similar to their Caucasian American counterparts. Moreover, the incidence of hip fractures is increasing throughout Asia, with a 2-fold increase observed over the past 30 years, and with the greatest increases observed in highly urbanized regions. Of course, the potential influence of changing incidence reporting and hospitalization patterns cannot be excluded from this finding.

The importance of nongenetic factors in hip fractures is also seen in the similarity in incidence reported for Hawaiians of Japanese versus Caucasian descent, despite the significantly lower frequency of hip fractures in Japan as compared with those reported for Caucasians residing in North American and Northern Europe.[38] Conversely, a University of California study suggested that differences in hip fracture rate between blacks, Asians, and Caucasians might have some relationship to the length of the hip axis.[39] These investigators found that mean hip axis lengths of Asian and black women are significantly shorter than that of Caucasians and concluded that this difference may contribute to the interracial disparity in the incidence of hip fractures.

Meissel et al[27] discuss the importance of both intrinsic and extrinsic factors in determining the relationship between the responses to therapy versus genetic traits. They note the large number of interstudy contradictions observed across disease conditions when attempting to define an association between genetic polymorphism and disease outcome. At least in part, ethnic back-

ground, gene-gene interactions, and gene-environment interactions are potential confounding factors that can bias conclusions derived from clinical investigations. Thus, ethnicity, genetics and environment are all important variables that can impact international differences in disease expression and therapeutic outcomes.

During the audience discussion, debate revolved around the potential dangers associated with the use of genetic test results for selecting a study population. This kind of selection procedure could potentially serve as a mechanism for manipulating study outcome. For example, if poor drug metabolizers were excluded from a study, the results of the investigation would not adequately predict product safety or efficacy across the entire spectrum of the potential patient population. On the other hand, understanding these differences may better explain the underlying causes for international differences in study outcomes. One example of this pertained to a gender and ethnic trait with CYP 2B6 that appears to be expressed to a much greater extent in women than in men, particularly women of Hispanic origin (E. Schuetz, personal communication). Thus, if the drug were eliminated via the CYP 2B6, lower drug concentrations may be observed in that subpopulation, which could either negatively impact drug effectiveness or suggest a greater than expected margin of safety (from a dose-response perspective).

On the other hand, it was recognized that the collection of genetic or biomarker information could facilitate the interpretation of clinical trial results and the extrapolation of these results across populations within a global marketplace. Meissel et al[27] even suggested that pharmacogenetic information could be used to stratify or select study participants to reduce sample size. Likewise, they suggested that DNA banks could be established during drug development or postmarketing surveillance studies to allow for pharmacogenetic parameters to be evaluated retrospectively.

Conversely, there are ethical concerns that need to be considered. In particular, the gathering of such information is complicated by ethical issues, and there needs to be assurance of informed consent prior to the collection of these data. The adequacy of ethical care of subjects and of informed consent is a principal concern of the ICH GCP guideline and the Declaration of Helsinki (GCP paragraph 2.1). However, there is concern that some jurisdictions may not be in full compliance with these principles (eg, providing financial incentives to entice people from impoverished areas).

Within the United States there is a concern about profiling and the stigmatization of identified communities. For example, within the Los Angeles region, Hispanic (Mexican) Americans were concerned that their DNA test results would be made available to the Bureau of Citizenship and Immigration. There is the recognition that we need to ensure that members of all populations have an opportunity to participate and benefit from publicly funded research.

There are several online resources that may be valuable to those interested in exploring this area further:

- *AAPS PharmSci* has an online special issue titled *Pharmacogenetics-Pharmacogenomics Virtual Journal*. This issue can be accessed at: http://www.aapspharmsci.org/theme_issues/virtual/index.asp (David J. Owen and Wolfgang Sadée, editors, accessed August 2003). This journal provides MEDLINE search results on such topics as trends in pharmacogenetics and pharmacogenomics, gene variants in disease and therapy, and clinical applications and drug therapy, genomics and proteomics.
- The Pharmacogenetics and Pharmacogenomics Knowledge Base (PharmGKB), which that is financially supported by grants from the National Institute of General Medicine (NIGMS), the National Heart, Lung, and Blood Institute (NHLBI), the National Human Genome Research Institute (NHGRI), the National Institute of Environmental Health Sciences (NIEHS), the National Cancer Institute (NCI), and the National Library of Medicine (NLM) within the National Institutes of Health (NIH). PharmGKB is managed at Stanford University. This work is supported by the NIH/NIGMS Pharmacogenetics Research Network and Database (U01GM61374). This database can be accessed at: http://www.pharmgkb.org/do/serve?id=home.welcome (accessed August 2003) and is intended to provide an integrated resource about how variation in human genes can lead to variation in drug response. A number of examples of the relationship between gene pattern and drug response, as well as an examination of ethical questions pertaining to the cataloguing of patient genetic data, are discussed in a recently published article by Dr J. Glasel.[40]

International Differences in Prescribing/Drug Use Practices: Its Impact on Clinical Trial Design

Agnes Klein, MD, Director, Clinical Evaluation Division, Health Canada

Among the various points already mentioned, variation in international trial results can reflect international differences in study interpretation and medical practices. Similarly, factors that may influence regulatory decisions within each nation include the prevalence of a disease, the spectrum of other available therapies, the availability of third party reimbursement, and the perception of acceptable risk/benefit ratios. Thus, final product approval often reflects the expectations of the society for which registration is sought.

The clinical response to a potential type of therapy is influenced by the many variables described by each of the presenters. These sources of international disparity in drug response affect the approvability of a product by the Canadian regulatory authorities. Examples include the following:

- Gp IIb/IIIa antagonists used in coronary artery disease.[41,42] One study demonstrated an absence of statistically significant differences between the test versus control drug. Further evaluation of these data showed that there were clear differences in drug response when administered to North Americans, but no differences when the test product versus control product were administered to either Europeans or South Americans.
- Outcomes in coronary artery disease: In comparing the United States and Canada, the United States fared better than Canada because of the use of earlier and more aggressive treatments. This led to an improvement in symptoms and survival within the United States. However, Canadians generally fared better than did their European counterparts.[43]
- Dyspepsia: The Canadian diagnosis of dyspepsia is very different from that of other countries, with Canadian definitions being more closely aligned with United States definitions as compared with European definitions. The Rome II consensus conference[44] and the American Gastroenterological Association medical position statement[45] do not include reflux disease within dyspepsia. However, the Can-Dys Working Group did not consider this distinction to coincide with the conceptual framework followed by primary care physicians when patients present with uninvestigated dyspeptic symptoms. Thus to reflect the reality of primary care, the Can-Dys Working Group consensus was that reflux disease is an integral constituent of uninvestigated dyspepsia.[46]

Even within North America, we find major differences in the organization of the United States vs Canadian Health Care systems and in patient care.[47,48] As compared with their United States counterparts, Canadians tend to spend a smaller percentage of Canada's gross domestic product on health care, and the Canadian government exerts greater control over health expenditures.[49] In Canada, patients tend to have longer hospital stays but fewer invasive cardiac procedures. For example, in the late 1990s, approximately 51% of the Canadian patients admitted to a coronary care unit presented with an acute MI, as compared with only 35% of those admitted within the United States. Despite similar patient clinical characteristics, coronary arteriography was performed in 68% of the United States patients, as compared with 35% of those from Canada. Regional differences were also observed in the use of follow-up procedures.

Despite these differences in practice philosophy, there was no perceptible difference in 1-year patient mortality (22% in Canada versus 23% in the United States) or the rate of reinfarction (14% in Canada versus 13% in the United States).[47,48] The only significant differences in patient health were noted in the higher incidence of activity limiting angina in Canada (33%) versus the United States (27%) and in the 6-month mortality associated with unstable angina.[50] Similar findings were noted with regard to the treatment of aneurysmal subarachnoid hemorrhage.[49] It has been hypothesized that, at least in part, differences in patient care may reflect differences in reimbursement systems, which provide United States hospitals and patients with the incentive for shorter hospital stays, use of nursing home and rehabilitation facilities, and greater use of in-hospital procedures.[49]

While most national drug regulatory agencies consider the clinical science aspects for determining market approval, within Canada and the United States, state or province governing bodies also impact the availability of prescription drugs to certain patient groups. For example, reimbursable costs covered by Medicare may limit the availability or use of certain therapeutic alternatives by senior citizens. Similarly, the United States Veterans Administration has rules on drug products whose costs will be covered for retired veterans. Within that framework, the government remains involved not only with product effectiveness (through the regulatory approving bodies such as Health Canada and

the FDA), but also with product cost and the acceptability of therapies.

Within Canada, experiences with Enbrel (etanercept) and Remicade (infliximab) illustrate the effects that policy can have on physician prescribing practices. Both drugs are approved in Canada, and both have received strong endorsements as second line treatments from the Canadian Rheumatology Association.[51] While most private health care plans cover these drugs, the majority of provincial plans do not (eg, Ontario).[52] As it is the provincial formularies that generally cover the cost of prescription drugs for seniors and welfare recipients, these patients are, in effect, denied access to these medications.

The various Canadian medical associations have developed Clinical Practice Guidelines[53] for many diseases and disorders. The Canadian Medical Association (CMA) Infobase is a database generated by the CMA. It contains 2000 records of guidelines that are either produced or endorsed within Canada by national provincial/territorial or regional medical or health organizations, professional societies, government agencies, or expert panels.[54] Examples of disease-specific Clinical Practice Guidelines include osteoporosis, diabetes, and dyslipidemias. The database includes consensus statements for the treatment of such conditions as *Helicobacter pylori*, reflux esophagitis, and peptic ulcer. In general, these Guidelines and consensus statements focus on the management of specific disease conditions and disorders. It is within this context that pharmacotherapy is defined, and drug classes may be classified as either first- or second-line treatments for the various disorders. [55]

While these Guidelines should be considered in the design of clinical studies, they are not considered to be official government (Health Canada) documents. Generally, the federal government was accorded observer status but did not actively participate in the development of the Guidelines. Accordingly, while these Canadian Guidelines may differ from those established by medical authorities within the United States or Europe, Health Canada will generally not reject a study based upon somewhat different endpoints with respect to clinical expectations (eg, the targeted blood lipid levels to achieve when treating dyslipidemias). In that regard, good science is more important than minor regional differences. Nevertheless, to avoid potential problems in study acceptability, sponsors are strongly encouraged to consult with Health Canada before initiating a clinical trial.

Examples of Guidelines are as follows:

Fodor JG, Frohlich JJ, Genest Jr JJ, McPherson PR, for the Working Group on Hypercholesterolemia and Other Dyslipidemias. Recommendations for the management and treatment of dyslipidemias. CMAJ. 2000;162(10):1441-1447.

Meltzer S, Leiter L, Daneman D, et al. Clinical practice guidelines for the management of diabetes in Canada. CMAJ. 1998;159(suppl 8):S1-S29.

Rowe T, Lea RH, Belisle S, et al. The Canadian consensus of menopause and osteoporosis–2002 update. J Obstet Gynaecol Can. October 2002;24(10):108.

There are occasions when international differences in therapeutics and in clinical practice situations challenge the ability to extrapolate therapeutic inferences from clinical trials conducted outside of Canada. For example, returning to the issue of dyspepsia, the Canadian consensus Guidelines concerning the diagnosis and treatment of *H pylori*[56] have had 2 updates for special situations,[57] one concerning approaches in children[58] and another on limitation of expensive diagnostics.[58] In general, the recommended course of therapy involves polypharmacy, including the use of a proton pump inhibitor or ranitidine plus bismuth citrate plus 2 anti-infectives, such as amoxicillin and clarithromycin, or alternatively metronidazole plus clarithromycin.[44,56] Guideline advice on treatment strategies included some extrapolation of *H pylori* clinical trial eradication results from other countries, which further involved an allowance for differences both in drug substance and *H pylori* resistance to metronidazole treatment.[59] In Canada, only bisthmuth subsalicylate is available, although data from other countries of bismuth adjunct treatment involved the use of colloidal bismuth subcitrate.

Regarding differences in microbial susceptibility, there are wide geographic differences in prevalence of *H pylori* resistance to metronidazole. Such variations can even be seen within Canada (eg, 18% in Quebec and 38% in Nova Scotia). Thus, the recommendation for the use of 2 antimicrobial agents, amoxicillin plus clarithromycin, in conjunction with a proton pump inhibitor is not surprising. In fact one study with clarithromycin alone as the anti-infective achieved the highest *H pylori* eradication rate (54%) for a single agent,[60] although 90% eradication results were obtained when amoxicillin or metronidazole double antibiotic therapy was administered.[61] An additional complication is that foreign trials administered 400 mg of metronidazole, although 500 mg is the usual dose used in Canada.[60]

With regard to biologics, these applications are associated with problems distinct from those associated with most drug product applications, and the quality aspect of drug development has a more significant impact on the clinical performance of biologics as compared with pharmaceuticals. As discussed in the ICH guideline concerning safety testing of biotechnology-derived products,[62] the immunological properties of monoclonal antibodies need to be described in detail. This includes information pertaining to their antigenic specificity, complement binding, and any unintentional reactivity and/or cytotoxicity toward human tissues distinct from the intended target. It is further recommended that cross-reactivity studies be carried out using appropriate immunohistochemical procedures and a range of human tissues.

Companies pursuing biologics tend to be smaller than the large pharmaceutical conglomerates, thereby facilitating interaction between these companies and Health Canada. However, within the past 2 years, an increased interest in the development of these products has resulted in an evolution in the process for evaluating biologics within Canada. It has led to the creation of the Biologics and Genetic Therapies Directorate in Canada on April 20, 2000.

International Differences in Pathogen Susceptibility (Bacterial, Parasite, Etc.): Implications for the Use of Foreign Data

William A. Craig, MD, Professor of Medicine, University of Wisconsin

One of the drug classes posing the greatest challenge to the globalization of clinical data is anti-infective products. In addition to the concerns raised for all other drug classes, anti-infective products are associated with an additional level of complexity: the potential for regional differences in pathogen distribution, pathogenicity, and susceptibility. In an attempt to better understand these differences, there are an increasing number of large multicenter surveillance studies from hospitals in Europe, North America, Latin America, and Asia-Pacific regions.

Generally, the causative pathogens associated with specific disease processes are similar across the globe. For example, the vast majority of skin and soft tissue infections are associated with gram negative bacilli (GNB) and *Staphylococcus aureus*. An estimated 32% of the skin and soft tissue infections are associated with *S aureus* in Latin America, 47% of skin and soft tissue infections are associated with *S aureus* in Asia-Pacific region. The fewest number of these infections are attributable to *Streptococcus spp*.[63,64] *S aureus* is also found to be the most frequently isolated pathogen causing bloodstream infection in the United States, Canada, and Latin America, and coagulase-negative *Staphyloccocus* species (CoNS) are the third most common cause of bloodstream infections.[64] Similar geographic comparability is observed for infections associated with *Pseudomonas aeruginosa*.[65]

In contrast to the international similarity in pathogen-disease relationships, there exist marked differences in the susceptibility of pathogens (fungal[66] as well as bacterial[64]). For example, there is a very marked difference in the percentage of *S aureus* isolates that are methicillin resistant (MRSA). Across the United States, Canada, Latin America, Europe, and Asia-Pacific, the lowest percentage of MRSA was found in Canada (eg, 4% of *S aureus* bloodstream infections), the highest was consistently seen in the Asia-Pacific countries (eg, 44% for *S aureus* bloodstream infections). Across the United States, Latin America, and Europe, with the exception of skin and soft tissue infections, the highest percentage of MRSA isolates was found in the United States.[64] The percentage of total isolates found to be methicillin resistant for individual countries across the 3 regions (Western Hemisphere, Europe, and Western-Pacific centers) are provided in **Figures 1-3**. It should be noted that all antimicrobial susceptibility testing was performed using broth microdilution methods described by the National Committee for Clinical Laboratory Standards (NCCLS).

Slightly different patterns of regional susceptibility differences were seen with *Pseudomonas aeruginosa*.[65] Using susceptibility testing procedures consistent with NCCL criteria and isolates obtained in 1999, Latin America was generally associated with the least susceptible isolates to the various classes of antimicrobial compounds, followed by Europe. The lowest rate of drug resistance was observed in Canada (**Figure 4**).

The mechanism responsible for the development of drug resistance can differ markedly between countries.[65] Depending upon the mechanism involved, there can be cross-resistance to other antimicrobial compounds, thereby leading to marked regional differences

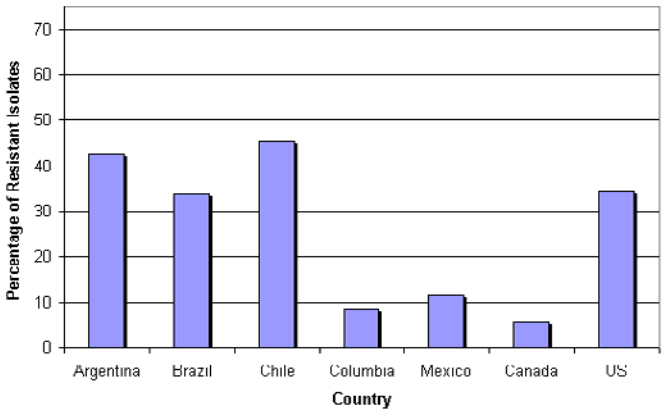

Figure 1. Rates of methicillin resistance among *Staphylococcus aureus* isolates in the Western Hemisphere SENTRY centers, 1997-1999 (based upon data provided by Diekema et al).[64]

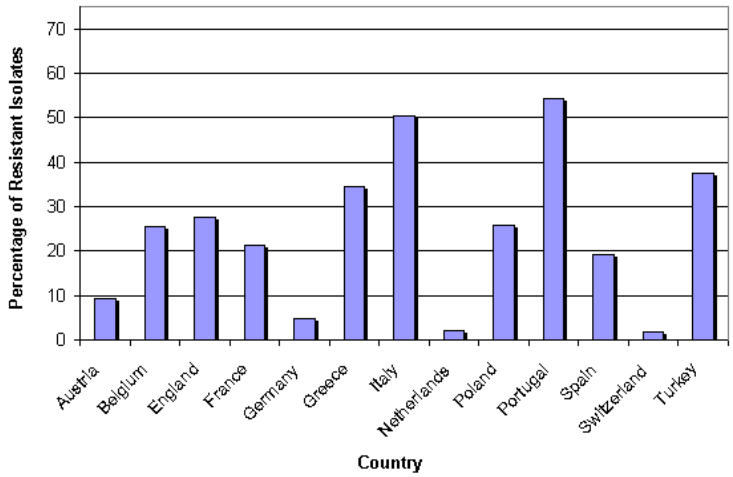

Figure 2. Rates of methicillin resistance among *Staphylococcus aureus* isolates in the European SENTRY centers, 1997-1998 (based upon data provided by Diekema et al).[64]

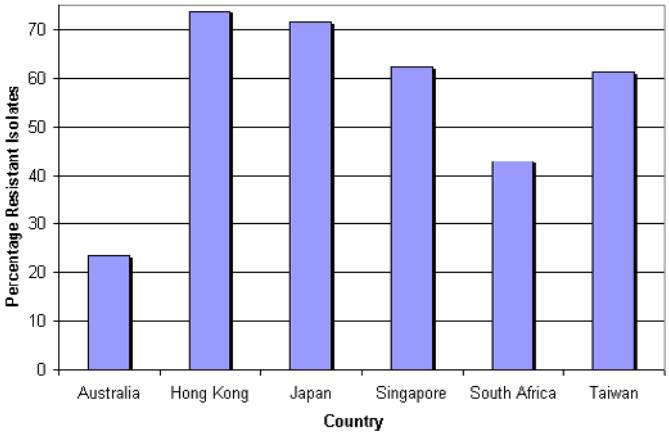

Figure 3. Rates of methicillin resistance among *Staphylococcus aureus* isolates in the Western Pacific SENTRY centers, 1997-1999 (based upon data provided by Diekema et al).[64]

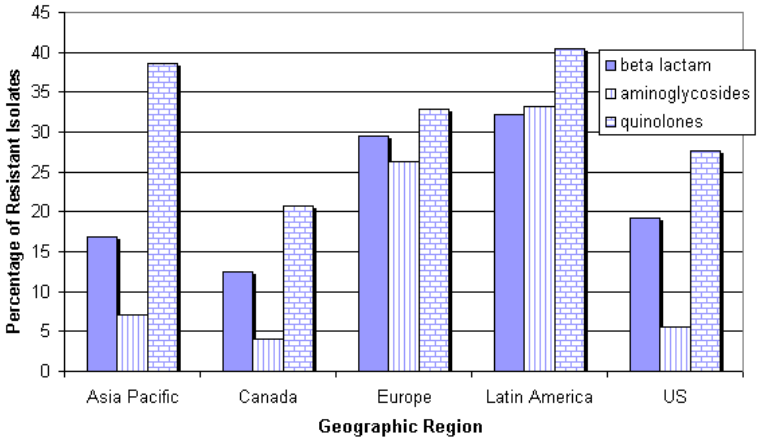

Figure 4. Rates of *Pseudomonas aeruginosa* isolates found resistant to the various drug classes as a function of geographic region (based upon data provided by Gales et al).[65]

in the pattern of drug cross-resistance patterns. The percentages of MRSA isolates co-resistant to gentamicin range from 25.9% in Canada to 91.2% in Latin America. Even within geographically close regions, differences can occur. Within the United States there was a substantially higher percentage of MRSA isolates co-resistant to ciprofloxacin (88.6%) and erythromycin (92.7%) as compared with Canada (60.5% and 75.3% for ciprofloxacin and erythromycin, respectively) during that same survey period (1997-1999).[64]

The various mechanisms that may be involved in the development of resistance include the following[65]:

- β-lactamase resistance due to AmpC β-lactamase production.
- Extended-spectrum β-lactamase production.
- A barrier to drug diffusion through the outer bacterial membrane.
- Efflux mechanisms.
- Loss of permeability of the drug (eg, porin closure).
- Alterations in DNA gyrase.
- Presence of aminoglycoside-modifying enzymes, leading to the emergence of multidrug resistance.

These differences in resistance mechanism can impact not only the selection of appropriate pharmacotherapy but also the pathogenicity of the microbial vector. This

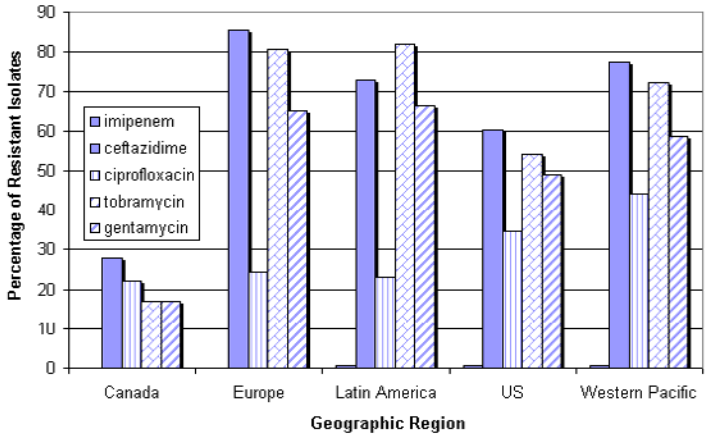

Figure 5. Rates of *Klebsiella pneumoniae* isolates found resistant to the various drug classes as a function of geographic region (based upon data provided by Winokur et al).[69]

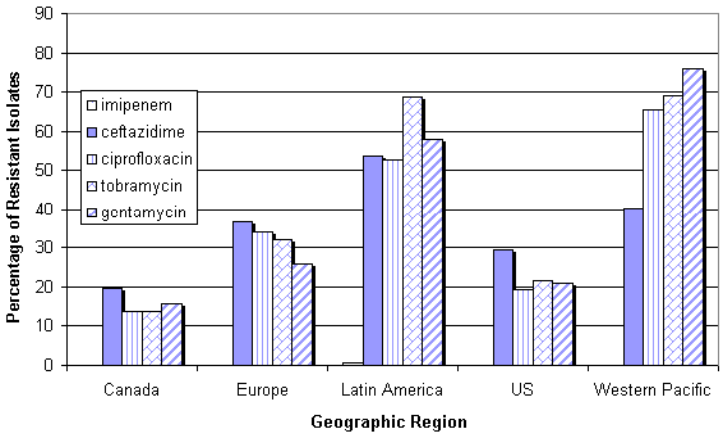

Figure 6. Rates of *Escherichia coli* isolates found resistant to the various drug classes as a function of geographic region (based upon data provided by Winokur et al).[69]

point raised the question of whether or not this difference in resistance mechanisms can result in differing levels of bacterial pathogen virulence across regions. Dr Craig indicated that he is currently examining this question. If pathogenicity and virulence vary, we would also anticipate a difference in disease progression and, consequently, differences in drug response. Considering the possible differences in bacterial virulence, pathogenicity, and drug susceptibility patterns across geographic regions, we can clearly see the potential not only for differences in the effectiveness but also differences in the efficacy of the positive control.

There tends to be much greater geographic variation in susceptibility patterns associated with Gram - than with Gram + organisms. For example *Klebsiella* has an enzyme that destroys antibiotics. Latin America, Europe, and Asia have higher levels of microbes with this enzyme than do the United States and Canada. Accordingly, if *Klebsiella* is a targeted pathogen, the geographic region within which the study is conducted may impact clinical outcome.[67,68]

Considering these differences in microbial susceptibility patterns, pathogen susceptibility test results should be provided if foreign data are to be used to support drug registration. Such information could improve the information available on the impact of that drug on resistant microbial strains and may also help to resolve one of the problems associated with the majority of study protocols: the use of resistance as one of the exclusion criteria.

Reasons for failing to collect pathogen samples often relate to regional differences in the use of diagnostic test procedures. In the case of otitis media, punctures are often not required, thereby restricting the ability of the investigator to collect pathogen samples. In the case of pneumonia, 50% to 60% of the clinical cases are handled in outpatient clinics. Therefore, investigators do not gather information on the pathogen load within the bronchial secretions. Similarly, susceptibility data are often lacking for fungal infections, viral infections, many HIV infections, and many parasitic infections.

Clearly, the compound selected as the positive control must be region-appropriate. For example, if there is a large number of extended spectrum beta lactamase (ESBL) strains, there tends to be a high level of coresistance to aminoglycosides, tetracyclines, trimethoprim-sulfamethoxazole, and ciprofloxacin. Accordingly, the positive control should be a carbepenem instead of a penicillin or cephalosporin for testing the effectiveness against Gram - pathogens.[69] In this regard, 45% of the strains in Latin America are ESBL. If there is a high incidence of macrolide resistance in pneumococci, then macrolides should not be the compound used as a positive control for outpatient respiratory infections such as community acquired pneumonia (CAP). Examples of differences in resistance patterns for *Klebsiella pneumoniae* and *Escherichia coli* are provided in **Figures 5** and **6**.

Differences in susceptibility patterns can influence the use of foreign data by:

- Reducing the efficacy of the test product and its comparator, thereby increasing the delta above acceptable values.
- Reducing the effectiveness of the comparator, thereby providing an inappropriate benefit to the test compound.

- Reducing the apparent effectiveness of the study compound, resulting in inferiority as compared with the positive control.

Models such as the Poole Therapeutic Outcome Model (developed by Dr Michael Poole, Houston, TX, http://www.vlmed.com/ABRS.htm) (accessed August 2003) or Monte Carlo simulations may assist in understanding the impact of changing microbial susceptibility patterns on the outcome of clinical trials. The Poole Therapeutic Outcome model integrates such variables as the proportion of subjects presenting with symptoms that are culture positive, the distribution of pathogens in the culture-positive group, the rate of spontaneous resolution for each pathogen, and the susceptibility of the pathogen to the antimicrobial agent. On the basis of these assumptions, the influence of changing susceptibility patterns on trial outcome can be determined. An example is provided below.

1. Success among culture-negative controls is estimated based on the proportion of culture-negative subjects and the rate of clinical resolution for the culture negative patients. For this example, we will assume that 40% of the patients are culture negative and that there is an 88% spontaneous resolution associated with these patients.
2. Success among culture positive subjects is estimated based on the following
   a. The proportion of subjects in the trial that are culture positive. For the sake of this example, we will assume that 60% of the patients are culture positive.
   b. The relative distributions of pathogens that are isolated in the clinical trials from these culture-positive subjects. For the sake of this example, we will assume that each patient is infected by a single pathogen, with the following overall distribution within the trial:
      (1) 42% *Streptococcus pneumonia*
      (2) 35% *Haemophilus influenzae*
      (3) 5% *Moraxella catarrhalis*
      (4) 18% others
   c. The rate of spontaneous resolution for the culture-positive patients. For the sake of this example, we will use the following values:
      (1) 30% *S pneumonia*
      (2) 60% *H influenzae*
      (3) 80% *M catarrhalis*
      (4) 50% others
   d. The proportion of the pathogens that are susceptible to the antimicrobial agent based upon pharmacokinetic/pharmacodynamic breakpoints. The model assumes that all patients with these susceptible organisms will be cured. For the sake of this example, we will use 2 sets of susceptibility values:
      (1) Trial A: Nearly all pathogens are susceptible
         (a) 90% *S pneumonia*
         (b) 90% *H influenzae*
         (c) 95% *M catarrhalis*
         (d) 80% others
      (2) Trial B: Some pathogen strains are found to be resistant
         (a) 30% *S pneumonia*
         (b) 50% *H influenzae*
         (c) 50% *M catarrhalis*
         (d) 50% others

With these values, we can estimate the impact of altered susceptibility on clinical outcome using the following equation:

(1) Culture negative % success = % culture negative × spontaneous cure of culture negative infections

(2) Culture positive % success (must be summed across all pathogens):

% culture positive patients × % with pathogen in question × (% pathogens susceptible to drug) + (% not susceptible to drug × spontaneous resolution for each pathogen).

Therefore, the expected results of the Trials A and B, based upon the assumptions provided above, are as follows:

Trial A

Culture negative spontaneous cure rate = 40% × 88% = 35.2%
S pneumonia = 60% × 42% × [90% + (10% × 30%)] = 23.4%
H influenzae = 60% × 35% × [90% + (10% × 60%)] = 20.2%

M catarrhalis = 60% × 5% × [95% + (5% × 80%)] = 3.0%
Others = 60% × 18% × [80% + (20% × 50%)] = 9.7%
Predicted success = 91.5%

Trial B

Culture negative spontaneous cure rate = 40% × 88% = 35.2%
S pneumonia = 60% × 42% × [30% + (70% × 30%)] = 12.9%
H influenzae = 60% × 35% × [50% + (50% × 60%)] = 16.8%
M catarrhalis = 60% × 5% × [50% + (50% × 80%)] = 2.7%
Others = 60% × 18% × [50% + (50% × 50%)] = 8.1%
Predicted success = 75.70%

The efficacy of antimicrobial compounds is aligned with both patient pharmacokinetics and the dynamics of the pathogen response to these concentrations. This response is generally described in terms of the minimum concentration needed to inhibit the growth of the pathogen (MIC). There is a wide range of tests that can be used to describe MIC values, and therefore, standardization of the methodology is critical. Within the United States, susceptibility testing is based upon standards set by the National Committee for Clinical Laboratory Standards (NCCLS). This is a globally recognized, voluntary consensus standards-developing organization that enhances the value of medical testing within the healthcare community through the development and dissemination of standards, guidelines, and best practices. NCCLS develops and publishes standards and guidelines through a unique consensus process involving government, professions, and industry. All NCCLS consensus documents are voluntary, but in certain instances, regulatory agencies or accrediting bodies will require that a specific NCCLS standard or guideline be followed. Information regarding the NCCLS can be obtained at www.NCCLS.org (accessed: August 2003). However, it should be noted that not all nations accept NCCLS standards. Therefore, discrepancies in study interpretation can occur.

Unlike many of the other classes of therapeutic agents, the evolving problem of emerging resistant strains renders it difficult to use the data from foreign trials. However, with the global spread of resistance, the international harmonization of drug use practice for anti-infective products is imperative. Given the ease with which individuals and goods can cross international boundaries, the transfer of pathogens is inevitable. Modeling efforts, such as use of the Poole Therapeutic Outcome Model and Monte Carlo simulation can help scientists better understand the impact of these changing susceptibility patterns. Unless global strategies are developed to control the emergence of resistant strains, there will eventually be no region unaffected by incurable infections. It will only be through a concerted international effort to optimize antimicrobial drug use practice that we can avoid facing an international crisis caused by the inability to effectively treat infectious diseases.

CONCLUSION

The increase in international mobility and growing global marketplace has rendered the concept of international harmonization of pharmaceutical trials to be an important consideration to regulators, drug sponsors, and end users. However, barriers to such harmonization efforts will continue to exist, both from variations among regions in clinical/societal issues, as well as from chemistry, manufacturing, and specification issues. Among the many variables that can affect the clinical outcome of an investigation are genetic polymorphism, nutrition, age, environmental conditions, pathogen susceptibility, societal values, and regional differences in medical practice. To facilitate harmonization, the use of global databases may provide an invaluable mechanism to help investigators tease out the critical variables that can influence therapeutic outcomes. This information should also help to identify those societal, environmental, and practice differences that cannot be controlled but may interfere with the acceptance or extrapolation of foreign clinical data. Nevertheless, insight into the factors influencing therapeutic responses will improve international drug availability, global product uniformity, and the dosing strategies to optimize disease treatments.

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APPENDIX

ICH Efficacy Topics and Guidelines (Based upon information contained within www.ich.org/ich5e.html**)**

1. Exposure

E1: The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions. This guideline provides recommendations on the numbers of patients and duration of exposure for the safety evaluation of drugs intended for the long-term treatment of non-life-threatening conditions.

2. Clinical Safety

E2A: Definitions and Standards for Expedited Reporting. This guideline provides standard definitions and terminology for key aspects of clinical safety reporting. It also gives guidance on mechanisms for handling expedited (rapid) reporting of adverse drug reactions in the investigational phase of drug development.

E2B: Data Elements for Transmission of ADR Reports *Step 5*. This guideline provides standard definitions and terminology for key aspects of clinical safety reporting. It also gives guidance on mechanisms for handling expedited (rapid) reporting of adverse drug reactions in the investigational phase of drug development.

E2B(M): Maintenance of the ICH Guideline on Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports. The E2B topic was a highly successful effort to define the data elements necessary for the exchange of individual case safety reports electronically. Pilot studies indicated the feasibility of the transactions but also identified areas that could be improved by further discussion in the expert working group.

E2C: Periodic Safety Update Reports. This guideline gives guidance on the format and content of safety updates, which need to be provided to regulatory authorities, at intervals, after products have been marketed. It is intended to ensure that the worldwide safety experience is provided to authorities at defined times after marketing with maximum efficiency and avoiding duplication of effort.

3. Clinical Study Reports

E3: Structure and Content of Clinical Study Reports. This guideline allows for a single compilation of worldwide core clinical study reports, for inclusion in applications to ensure more efficient generation and submission of data to the regulatory authorities.

4. Dose Response

E4: Dose-Response Information to Support Drug Registration. This guideline provides recommendations on the design and conduct of studies to assess the relationship between dose, blood levels, and clinical response in the early stages of the clinical development of a new drug.

5. Ethnic Factors

E5: Ethnic Factors in the Acceptability of Foreign Clinical Data. This guideline addresses the intrinsic characteristics of the drug recipient and extrinsic characteristics associated with environment and culture, which are likely to impact on the results of clinical studies carried out in different ethnic groups.

6. Good Clinical Practice

E6: GCP Consolidated Guideline. This is a consolidated document that defines a tripartite standard for the conduct of clinical trials. It covers aspects of preparation, monitoring, reporting, and archiving of clinical trials and incorporating addenda on the *Essential Documents* and on the *Investigator's Brochure*, which had been agreed upon earlier through the ICH process.

7. Clinical Trails in Special Populations

E7: Clinical Trials in Special Populations: Geriatrics. This guideline provides recommendations on the special considerations that apply in the design and conduct of clinical trials on medicines that are likely to have significant use in the elderly.

8. Clinical Trial Design

E8: General Considerations for Clinical Trials. This guideline defines the general scientific principles for the conduct, performance, and control of clinical trials. The guideline addresses a wide range of subjects in the design and execution of clinical trials and in the evaluation of the scientific validity of protocols.

E9: Statistical Principles for Clinical Trials. The issues in a biostatistical guideline affect each and every clinical trial contained in a dossier. Accordingly, this guideline is intended to overcome the differences in the level of detail required in the different ICH regions, which can be an obstacle to the general acceptance of analyses and conclusion from clinical trials.

E10: Choice of Control Group in Clinical Trials. This guideline addresses the choice of control groups in clinical trials needed for an approval of a dossier with respect to efficacy and safety. At present, there are major differences in practice and attitudes toward the need for placebo controlled trials (or other trials in which a difference between treatments is shown) and the acceptability of active control equivalence trials as evidence of efficacy and safety. This difference applies both to determinations of intrinsic efficacy and to the need for comparison with other drugs.

9. Pediatrics

E11: Clinical Investigation of Medicinal Products in the Pediatric Population. This addresses the conduct of pediatric trials on medicines. The existing guidances are based on differing assumptions and propose different strategies, scientific principles, and regulatory standards. The objective of ICH Guideline will be to facilitate the development of safe and effective use of medicinal products in children and help eliminate the current difficulties encountered by companies operating internationally.

10. Therapeutic Categories

E12A: Clinical Trials on Antihypertensives. This document focuses on the type of study designs and development phases that are common to all 3 ICH regulatory authorities. Since there are a few major differences in the requirements of the 3 regions, this document should be considered as an “ICH Principle Document” rather than an “ICH Guideline.” It will not be subject to the usual ICH Step Procedures leading to a fully harmonized document.